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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,837	09/04/2001	Kenya Shitara	249-188	4386

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,837	SHITARA ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/8/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group III (claims 22-28) in Paper No. 10/31/2003 is acknowledged. The traversal is on the ground(s) that the restriction requirement would not pose undue burden on the examiner. This is not found persuasive because the invention as claimed does provide a special technical feature which distinguishes or contributes over the prior art cited, and as such unity of invention is lacking. Furthermore, the search for the different inventions would pose an undue burden to search because the search for the methods would require a search in multiple, different, distinct, and ever-expanding databases that are not necessarily overlapping or co-extensive.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-28 are pending, claims 1-21 are with drawn from further consideration as being drawn to a non-elected subject matter. Applicant is reminded to cancel claims drawn to non-elected invention(s).

3. Claims 22-28 are examined on the merits.

Information Disclosure Statement

4. The Information Disclosure Statement filed 10/25/2001, 3/8/2002, (paper no. 3/08/2002) is acknowledged and considered. A signed copy of the IDS is attached hereto. Please note, reference EP 882799 is considered on the PTO-1449 filed 3/8/2002.

Claim Rejections - 35 USC § 112, 2nd paragraph

5. Claims 23-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 23-28 recites the limitation "anti-human VEGF receptor Flt-1 antibody" in claim 22. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 22-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable the skilled artisan to practice a method of treating a disease caused by a tumorigenic change of a hematopoietic cells, comprising the administration of an anti-flt1 antibody.

The instant invention is drawn to a method of treating a hematopoietic cell disorders, such as leukemia, comprising the administration of specific anti-flt1 antibodies.

The specification teaches that specific clones of an anti-flt1 antibody, namely, KM1730 and KM1732, were able to detect specific T-cell and non-T cell/non-B cell leukemias in vitro. What the specification has not disclosed to one of skill in the art is a method of treating diseases of hematopoietic cell origin, comprising the administration

of the anti-flt1 antibodies. It is well established in the art that the use of in vitro cultured cells for the determination of in vivo treatment options is not a predictable means of experimentation. The specification has only taught diagnostic methods, and there is insufficient guidance and objective evidence that such teachings would be indicative of tumorigenic changes of hematopoietic cells in-vivo, i.e. in an individual; wherein it would not be predictable to one of skill in the art to use the method in treat leukemia in any individual. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human therapeutic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems

involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 22-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,6,7,10, 34, and 49-50 of copending Application No. 10/160232 in view of claims 3-5, and 9 of co-pending Application No. 10/009723. The claims are drawn to a method of treating a disease caused by a tumorigenic change of a hematopoietic cell, comprising the administration to a patient of an amount of an anti-human VEGF receptor flt-1 (claim 22); wherein the anti-human VEGF flt-1 antibody is a monoclonal antibody (claim 23), of which is selected from a group which includes KM1732 (claim 24); wherein the said antibody is humanized (claim 25); wherein the antibody is selected from the group consisting of Fab, Fab', F(ab')2, single chain antibody, and a disulfide stabilized antibody (claim 26); wherein the antibody is fused to a radioisotope, a protein or a low molecular weight agent (claim 27); wherein the disease is leukemia (claim 28).

US Application No. 10/160232 (herein referred to as '232)claims a method of treating a disease comprising the administration of an antibody that binds to and reacts with human VEGF receptor flt-1. Application '232 also claims the KM1732 antibody and claims that said antibody can be humanized or antibody fragments consisting of Fab, Fab', F(ab')2, single chain antibody, and a disulfide stabilized antibody. Application '232 however, does not specifically characterize the hematopoietic disease claimed in the instant invention. This deficiency is remedied by US Application 10/009723 (herein referred to as '723), wherein it is claimed that a human VEGF receptor flt-1 antibody can

be used as a reagent that is capable of reacting with hematopoietic cells, wherein the antibody can be KM1732.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a human VEGF receptor flt-1 antibody for the treatment of a disease caused by tumorigenic changes of a hematopoietic cell. One of skill in the art would have been motivated to do so because application '232 taught that disease can be treated with an antibody directed against VEGF receptor flt-1 using specific antibodies (i.e. KM1732) and that one of these diseases may be diseases associated with tumorigenic changes to hematopoietic cells as taught by application '723.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Shitara *et al* (US Patent 6,617,160).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are drawn to a method of treating a disease caused by a tumorigenic change of a hematopoietic cell, comprising the administration to a patient of an amount of an anti-human VEGF receptor flt-1 (claim 22), wherein the anti-human VEGF flt-1 antibody is a monoclonal antibody (claim 23), of which is selected from a group which includes KM1732 (claim 24). Shitara *et al* teach a method of treating a disease through the administration of an anti-human VEGF receptor flt-1 antibody, wherein the antibody can be monoclonal (see column 4, lines 46-50), wherein the monoclonal antibody is KM1732 (see column 4, lines 19-20). The administration of the anti-human VEGF receptor flt-1 antibody as taught by Shitara *et al* would also inherently treat diseases associated with tumorigenic chages of hematopoietic cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

for:

Christopher Yaen
Art Unit 1642
December 3, 2003